The Frontoparietal Control System: A Central Role in Mental Health

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Abstract
Recent findings suggest the existence of a frontoparietal control system consisting of *flexible hubs* that regulate distributed systems (e.g., visual, limbic, motor) according to current task goals. A growing number of studies are reporting alterations of this control system across a striking range of mental diseases. We suggest this may reflect a critical role for the control system in promoting and maintaining mental health. Specifically, we propose that this system implements feedback control to regulate symptoms as they arise (e.g., excessive anxiety reduced via regulation of amygdala), such that an intact control system is protective against a variety of mental illnesses. Consistent with this possibility, recent results indicate that several major mental illnesses involve altered brain-wide connectivity of the control system, likely altering its ability to regulate symptoms. These results suggest that this "immune system of the mind" may be an especially important target for future basic and clinical research.

A fundamental mystery of clinical neuroscience is why some patients have much better outcomes despite similar neural or experiential disturbances (e.g., a virtually identical trauma). One major factor may be individual differences in cognitive control abilities—a set of cognitive processes that coordinate goal pursuit (Miller and Cohen 2001; Schneider and Chein 2003). We suggest that those individuals who are better able to pursue their goal of recovery are likely to experience better outcomes. This is consistent with the widespread observation of impaired cognitive control among those diagnosed with any of a variety of mental diseases (Diamond 2013). Extensive evidence suggests the existence of a cortical system that implements cognitive control (Cole and Schneider 2007; Duncan 2010). Thus, this control system's capacity may be an important factor in the maintenance and improvement of mental health. Here, we review findings that characterize the properties of the control system and introduce an integrative theory that postulates this system may play a central role in mental health.

Recent studies have begun to identify the basic properties of the control system. Such decomposition of the control system is critical for avoiding the homunculus (i.e., "little man") fallacy, wherein goal-directedness of a person is explained away by an undifferentiated internal entity that is nearly equivalent to another person. First, the control systems consists of distinct cortical regions that are highly interconnected (Cole and Schneider 2007; Thomas Yeo and others 2011; Vincent and others 2008)—consistent with the notion that this set of regions forms an internally differentiated yet unified system (Cole and Schneider 2007). Second, the control system is thought to consist of several subsystems (Fig. 1A)—defined as having especially high within-subsystem connectivity—that have related but not identical functions (Power and others 2011). For instance, the *frontoparietal* portion is thought to be especially involved in highly adaptive control processes, the *cingulo-opercular* portion is thought to be especially involved in time-extended control processes, and the *dorsal attention* portion is thought to coordinate attention to external stimuli (Corbetta and Shulman 2002; Dosenbach and others 2007). Third, the control system—especially the frontoparietal subsystem—has especially extensive brain-wide connectivity (Cole and others 2010; Power and others 2011) (i.e., its regions are hubs), suggesting it can communicate with a variety of systems throughout the brain. The ability for these hubs to communicate with many systems may be what allows them to be domain-general

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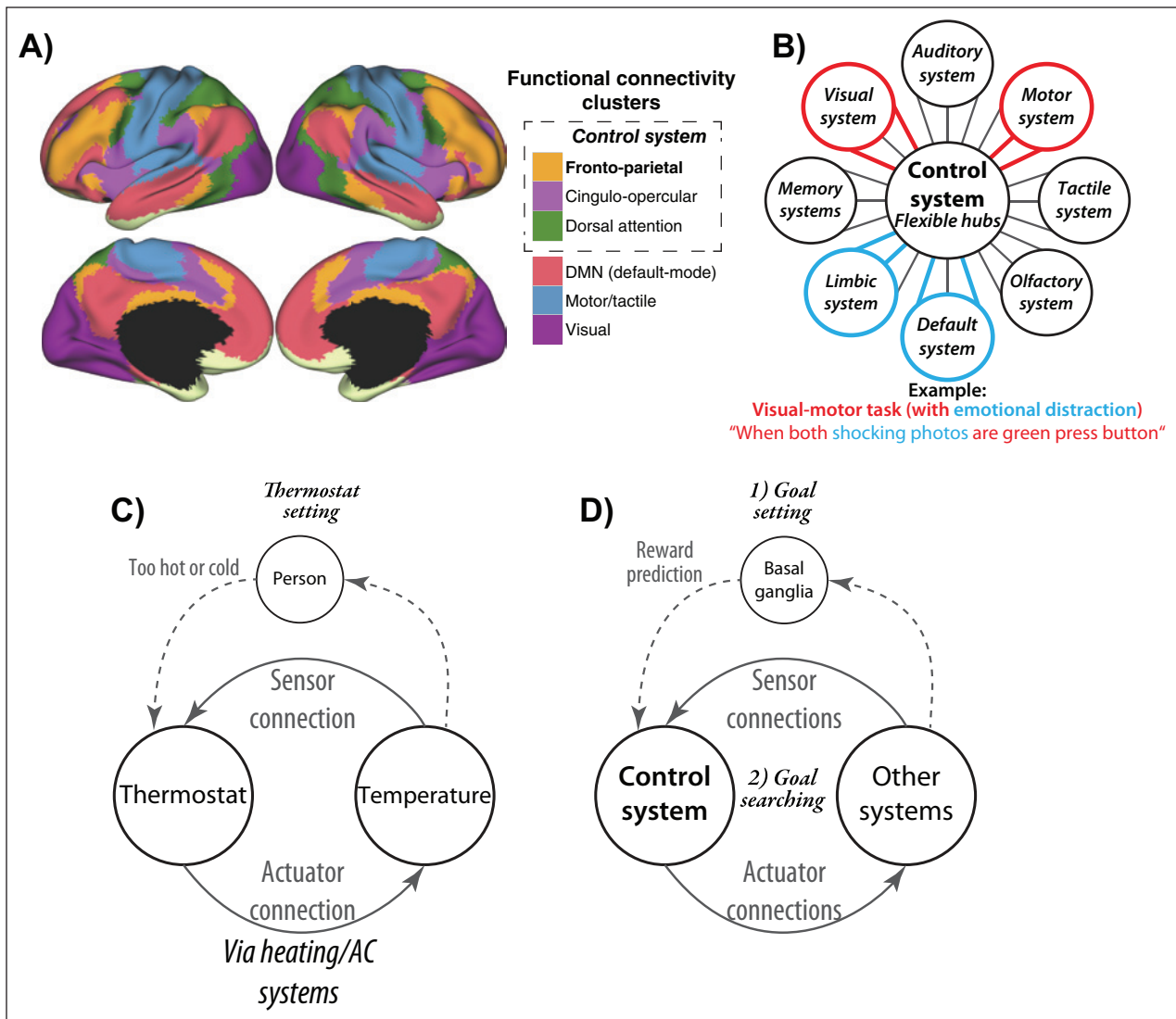Email: michael.cole@rutgers.edu

Figure 1. The control system and flexible hubs. (A) Clustering applied to resting-state functional connectivity MRI identified large-scale neural systems (Thomas Yeo and others 2011). Components of the control system are co-active in a wide variety of task domains (i.e., the system is domain-general) (Duncan 2010; Fedorenko and others 2013), are sensitive to a variety of cognitive control demands (Niendam and others 2012), and this system is split here into three subsystems. The frontoparietal subsystem is labeled in bold because of its centrality to adaptive task control (Cole and others 2013b; Dosenbach and others 2007), though all subsystems are highly interconnected and functionally related (Cole and Schneider 2007; Vincent and others 2008). (B) Recent evidence suggests the core control system has highly global functional connectivity (Cole and others 2010; Power and others 2011) that updates systematically across tasks (Cole and others 2013b). Furthermore, the control system inhibits the default-mode system when it is irrelevant to task performance (Chen and others 2013; Shulman and others 1997), and control system inhibition of the default-mode system is impaired in mental illness (Anticevic and others 2012a). (C) A schematic of how temperature is regulated by a thermostat (a controller in a feedback control loop). (D) Several biologically realistic computational models suggest a two-step process of cognitive control (Braver and Cohen 1999; O'Reilly and Frank 2006). The first is reward prediction by the basal ganglia selecting a goal representation via the control system. The second step involves goal maintenance with searching for subgoals to accomplish the goal (matching the current state to the maintained goal state representation). This is similar to feedback control in other contexts (e.g., controlling temperature with a thermostat).

(Chein and Schneider 2005; Fedorenko and others 2013) (e.g., involved regardless of sensory or motor modality). Fourth, the pattern of functional connectivity between the control system and a variety of other systems is updated

depending on current task demands (Cole and others 2013b; Sakai 2008). This suggests that the control system contains *flexible hubs*—brain regions that implement control via task-dependent biases of their connections

throughout the brain (Cole and others 2013a; Cole and others 2013b) (Fig. 1B).

It is currently unknown exactly how the control system's flexible hubs use adjustments in functional connectivity to implement control of distal systems. One parsimonious possibility is that flexible hubs implement control via feedback loops with a variety of brain systems, similar to how feedback control is implemented in many engineered and other biological systems (Fig. 1C and D). For instance, setting the temperature with a thermostat may be akin to (though simpler than) setting a goal in the control system, with the feedback between a temperature sensor (sensor connectivity) and the heating and cooling actuators (actuator connectivity) being used to search for—and eventually achieve—the goal. Similar mechanisms have also been postulated for the motor system's control of muscles (Diedrichsen and others 2010). Unlike a thermostat's univariate linear search (pushing the temperature up or down to match a single variable), however, the control system must perform multivariate nonlinear search (trying sequences of functional connectivity patterns) until a goal is achieved. Recent results suggest that previously learned functional connectivity patterns can be recalled and reused in new contexts and in novel combinations to facilitate this search process (Cole and others 2013b).

We suggest that these mechanisms may provide the control system with important computational properties for promoting and maintaining homeostatic balance across distributed neural systems, increasing optimal behavioral outcomes (i.e., mental health). In other words, the control system's ability to regulate other systems in a goal-directed manner (Cole and others 2013b) may lead it to reduce goal-disrupting processes as they arise and are manifest overtly as symptoms of mental disease (Fig. 2). This suggestion is based on two basic assumptions: first, that complex mental illnesses result primarily from dysregulated brain systems (i.e. they represent brain-based disorders) and, second, that these diseases are harmful/undesirable to the individual. This definition of mental disease is consistent with some of the most well established and influential theoretical arguments in the field (Henriques 2002; Wakefield 2007), including the "harmful dysfunction" hypothesis. Moreover, this definition is broadly in line with the National Institute of Mental Health (NIMH) conceptualization on mental illness (see Box 1).

If the first component of this definition is true (system dysfunction) then it is likely that the control system would be able to correct such dysfunction in many cases via the feedback control mechanism described above. However, what signals could the control system use to detect dysfunction of a distant system? This is where the second component of the definition becomes important
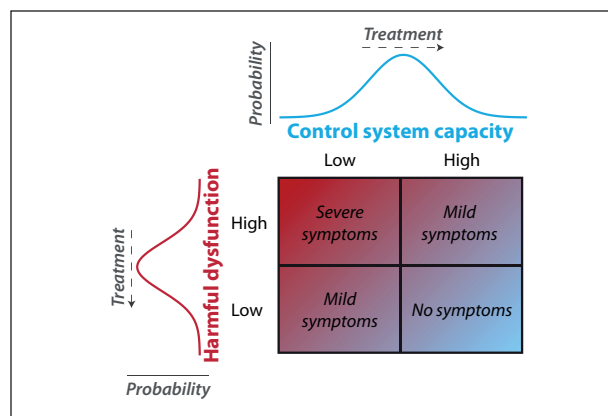

Figure 2. Control system capacity interacts with dysfunctions to regulate symptoms. Like the body's immune system is protective against symptoms of bodily disease, the control system is postulated to be protective against symptoms of mental disease—likely via the flexible hub mechanisms described above. Theoretical probability distributions are shown to indicate any given individual's likelihood of control system capacity (top) and the severity of a harmful dysfunction in any given mental process (left). The likely levels of experienced symptoms are indicated at different combinations of control system capacity and dysfunctionality. Treatment for each mental disease is postulated to be specific to that disease when harmful dysfunctions are reduced (left), but may be common across diseases when control system capacity is enhanced (top) because of the domain generality of the control system (Chein and Schneider 2005; Duncan 2010).

(that it is harmful/undesirable to the individual)—the control system is specialized for implementing goal pursuit, such that any undesirable dysfunction would, by definition, interfere with goal pursuit and become the target of regulation by the control system.

In summary, ongoing research into the basic properties of the control system is revealing neural mechanisms by which a variety of mental diseases may be regulated. In particular, it appears that the control system consists of flexible hubs that use feedback control (via dynamic global connectivity) to regulate processes in a variety of brain systems. Many goal-incompatible (i.e., undesirable/ harmful) processes contribute to the symptoms of mental diseases, such that the control system likely utilizes these flexible hub mechanisms to regulate symptoms and so promote mental health. Below we articulate the implications of this flexible hub theory, recent evidence relevant to the theory, along with testable hypotheses stemming from this framework. Note that in the text that follows, all references to the control system and flexible hubs are meant to map directly onto the mechanisms described in this section and illustrated in Figure 1.

The Importance of an Intact Control System Across Neuropsychiatric Conditions

The above theoretical argument suggests that an effective control system would be protective against a variety of mental diseases. Consistent with this view, a wide variety of mental diseases involve impaired cognitive control abilities [Barnett 2006] and altered control system functionality. Perhaps the most well-established evidence for control system alterations have been observed in schizophrenia (Anticevic and others 2012c; Barch and Ceaser 2012; Cole and others 2011; Van Snellenberg and others 2006). Similar evidence has been identified in bipolar disorder (Anticevic and others 2013b), obsessive-compulsive disorder (Anticevic and others 2013c), anxiety disorders (Sylvester and others 2012), eating disorders (Friederich and others 2013), autism (Poljac and Bekkering 2012), attention deficit hyperactivity disorder (Makris and others 2008), posttraumatic stress disorder (Blair and others 2012), and major depression (Lee and others 2012; Zhang and others 2011), through a combination of neuroimaging approaches. Each of these neuropsychiatric conditions involve complex and somewhat distinct mechanisms underlying their pathophysiology, which cause dysfunctions across a distinct set of neural systems (e.g., amygdala in anxiety disorders; orbitofrontal cortex and basal ganglia in obsessive-compulsive disorder) and in turn separable behavioral abnormalities. However, recent efforts—such as the Research Domain Criteria (RDoC) project (Cuthbert and Insel 2013)—have begun to characterize common features across mental diseases in addition to these categorical distinctions (Adam 2013) (see Box 1). Consistent with the RDoC framework, it appears that control system dysfunction may be a common factor cutting across a broad range of mental diseases.

Box 1 Mental Illness as a Spectrum of Dysregulated Systems

Every day millions of individuals are affected by mental disease worldwide. Progress has been made in identifying and characterizing mental disorders, but inadequacies in current classification schemes are becoming more apparent as prognosis and biomarkers fail to honor diagnostic boundaries. To address this problem, a major effort at the National Institute of Mental Health is underway to redefine diagnostic criteria in terms of brain circuits—the Research Domain Criteria or RDoC (Insel and others 2010). This paradigm shift—mirrored by several other proposals (Adam 2013)—suggests a reconceptualization of the field's rigid categorical diagnostic systems toward a more dimensional framework that is capable of combining levels of inquiry. The National Institute of Mental Health's RDoC initiative suggests that complex mental disorders are fundamentally brain-based disorders

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arising because of dysregulation across neural systems, possibly because of shared mechanisms (Cuthbert and Insel 2013). This initiative is designed such that identifying the biological mechanisms indicative of a given complex behavioral disturbance will better link individuals with the proper treatment and improve outcomes, like other areas of medicine. Consistent with the RDoC initiative's emphasis on cross-disease traits, deficits in cognitive control—the ability to influence thoughts and emotions in a goal-directed manner—have been identified in a variety of mental illnesses (Poljac and Bekkering 2012; Sylvester and others 2012). More directly relevant to RDoC, these cognitive control deficits have been linked to alterations in distributed neural system connectivity, providing a possible target for biomarker refinement (Fig. 3C). Here, we propose a neurocognitive hypothesis that crosses traditional diagnostic boundaries to help explain how a wide variety of symptoms may be exacerbated by disruptions in the functioning of a cognitive control brain system. Conversely, we hypothesize how effective functioning of the control system may be protective against mental illness generally. This aspect of the theory is congruent with the RDoC framework because it proposes a shared neural dysfunction across psychiatric conditions with distinct behavioral profiles. We propose that future work should focus on delineating the underlying computational mechanisms that give rise to control system disruptions that are shared versus distinct across neuropsychiatric conditions. For instance, recent studies implicate glutamatergic dysfunction (possibly at the *N*-methyl-D-aspartate receptor) as relevant for coordination of large-scale neural systems involved in higher cognition (Anticevic and others 2012b). Future studies are needed to link our system-level predictions with specific cortical circuit mechanisms operating in particular psychiatric conditions.

Rather than considering all mental diseases as equal, however, we suggest there may be two broad ways control system capacity interacts with the harmful dysfunctions underlying mental disorders. We hypothesize that in certain neuropsychiatric conditions control system disruption is itself one of the primary pathophysiological processes of the disease. Such *primary control* disorders (such as schizophrenia and bipolar disorder) likely involve larger reductions of control system capacity on average than other disorders (Barch and Ceaser 2012) (Fig. 3A). This account predicts that—like immunodeficiency diseases of the body—primary control disorders are especially difficult to treat (Goff and others 2011) because of the diseases' disruption of natural health-promoting regulatory processes. Furthermore, primary control disorders may result in dysfunctional control signals that actually exacerbate symptoms, rather than simply failing to reduce them (Cole and others 2011). Consistent with this primary control pathology, typical cognitive
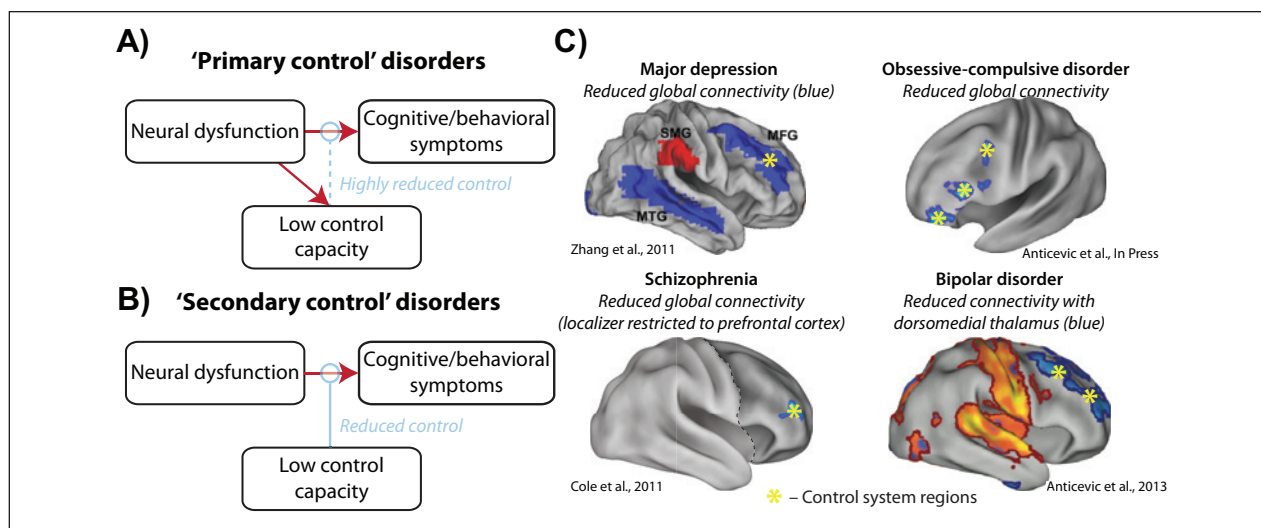
Figure 3. The control system is disrupted across mental diseases. (A) *Primary control* disorders are defined as involving neural dysfunction of the control system itself, such that control system capacity is more likely to be compromised in all individuals with such disorders. This predicts that primary control disorders are more difficult to treat because of the diseases' disruption of natural health-promoting processes. (B) In contrast, *secondary control* disorders are characterized as those that are exacerbated by low control system capacity (potentially by chance), but whose root neural dysfunction does not directly affect control system capacity. It may be possible, however, that if/when symptoms arise the control system capacity is in turn compromised (as a secondary downstream effect). (C) Resting-state functional connectivity (inter-region temporal correlations during rest) disruptions have been found with a key control system region—lateral prefrontal cortex (LPFC)—across a variety of mental diseases. LPFC's global connectivity (temporal correlations across all other regions) was altered in major depression (Zhang and others 2011), obsessive-compulsive disorder (Anticevic and others 2013c), and schizophrenia (Cole and others 2011). These alterations, as well as altered connectivity with a subcortical hub (mediodorsal thalamus) in bipolar disorder (Anticevic and others 2013b), are consistent with the flexible hub theory.

therapeutic approaches are much less effective for schizophrenia without concurrent pharmacological intervention (Lynch and others 2009).

In contrast, *secondary control* disorders are defined as mental diseases influenced by the natural variation in control system capacity across individuals (i.e., the general population distribution), without a given disease's underlying pathological processes causing direct reduction of control system capacity (Fig. 3B). Some examples of such secondary control disorders may include major depression, anxiety disorder, and obsessive-compulsive disorder (although future work is needed to verify this hypothetical division). Note, however, that there may be indirect disruption of the control system (e.g., major depressive episodes are associated with cognitive control deficits (Lee and others 2012)). In particular, it may be that the need to constantly regulate symptoms reduces the capacity of the control system for other cognitive demands (Anticevic and others 2012a). We develop this possibility further in a later section. Alternatively, it may be that individuals with especially effective control systems develop fewer symptoms (despite harmful dysfunctions) because of effective symptom regulation (see Fig. 2), such that studies of mental disorders (which depend on diagnosis based on overt symptoms) are biased to include predominantly those with lower-than-average control system capacity.

Consistent with a primary control disorder, there is strong evidence that the control system as a whole is affected in schizophrenia, though most evidence points to alterations of a key region in the control system—lateral prefrontal cortex (LPFC). Evidence for this comes from converging multidisciplinary work, such as postmortem studies of patients showing altered neurotransmitter and local microcircuit anatomy (Lewis and others 2005) as well as large neuroimaging investigations using both task-based (Repovs and Barch 2012) and resting-state (Fornito and others 2011) approaches. Consistent with these neural alterations affecting behavior, functional MRI (fMRI) studies have shown abnormal control system activation during cognitive control tasks in schizophrenia (Barch 2005). Furthermore, structural MRI studies have shown altered control system anatomy on a large scale as well (Zalesky and others 2011). Most relevant to the flexible hub theory, however, is the observation that LPFC's global connectivity is altered in schizophrenia patients relative to healthy comparison subjects (Cole and others 2011; Lynall and others 2010; Van Den Heuvel and others 2010) (Fig. 3C).

Again consistent with a primary control disorder, there is extensive evidence of control system disruption at multiple levels in bipolar disorder. For instance, post mortem studies have identified altered cellular composition within LPFC

and dorsal anterior cingulate in bipolar patients, and have associated this with emotional dysregulation (Green and others 2007). Furthermore, a recent study identified reduced functional connectivity between LPFC and a subcortical hub (mediodorsal thalamus) in bipolar patients (Anticevic and others 2013b) (Fig. 3C). Additionally, several control system regions were associated with an inability to modulate amygdala activity during emotional regulation among manic individuals (Foland and others 2008), consistent with reduced connectivity between LPFC and the amygdala in bipolar illness (Anticevic and others 2013a). In line with the primary versus secondary control distinction, there are common aspects to the genetics (Van Snellenberg and de Candia 2009), neurobiology (Anticevic and others 2013b), and cognitive control impairments (Green 2006) of bipolar disorder and schizophrenia.

A recent study examining obsessive-compulsive disorder found support for LPFC global connectivity disruption (Fig. 3C), in addition to disruption of connectivity in orbitofrontal cortex and basal ganglia (Anticevic and others 2013c). One possibility is that the core computational dysfunction causing this disorder involves orbitofrontal cortex and basal ganglia circuits, but that control system regions (such as LPFC) would have been able to correct that dysfunction had they been as well connected and well functioning as in healthy individuals. Alternatively, it could be that the difficulty of constantly regulating altered systems causes impairment (via cognitive loading) of the control system. We will explore these possibilities in a later section.

We have focused primarily on psychiatric disorders—how does the flexible hub theory relate to neurological conditions? A recent study demonstrated that control system integrity is important for recovering speech after aphasic brain lesions (Brownsett and others 2014). This is consistent with the control system using feedback control of remaining functionally intact language regions to facilitate recovery of speech in a goal-directed manner. This hypothesis makes the prediction that individuals with a robust control system may have improved outcomes from lesions of a variety of brain regions with a variety of possible functional deficits, regardless of specific modality (e.g., visual vs. language lesions). Furthermore, the flexible hub theory suggests that lesions of control system regions may be particularly debilitating to daily life (relative to other association cortex lesions) (Shallice and Burgess 1991), given the control system's domain-general role in goal-directed cognition.

Possible Feedback Control Mechanisms Relevant to Mental Health

Above we suggested that the control system uses feedback control, similar to many engineered systems (e.g., aircraft autopilot, car cruise control) and also similar to self-organizing and homeostatic feedback control in other biological systems (e.g., body temperature control, the body's immune system, ant colony organization) (Brun and others 2009). The key mechanism here involves the control system maintaining a goal state representation using *sensor* connections (brain connections that monitor goal-relevant signals) and *actuator* connections (brain connections that in turn affect the monitored signals). Another important mechanism relates to the control system's ability to search for functional (actuator) connectivity patterns that effectively modulate distributed neural computations to be more in line with the behavioral goal. It is likely that effective actuator connectivity patterns can be identified in several different ways.

Perhaps the most straightforward means for identifying actuator connectivity patterns is through direct feedback control (Fig. 4A). This involves direct monitoring of the to-be-regulated system via brain connectivity with the control system. For example, direct feedback control might be used when you decide to move your right index finger to press a button: (1) The goal may be set in the control system via the basal ganglia predicting reward (e.g., because you are thirsty and the button delivers a bottle of water), (2) the goal-associated functional connectivity pattern is loaded from long-term memory via existing (automatic) associations and sent to motor cortex, and (3) information from the motor and proprioceptive/tactile systems do not match the goal pattern so the control system sends another signal in a search for the correct signal until the goal is achieved. Something similar may happen, for example, during the regulation of anxiety in anxiety disorders. For instance, in the case of social phobia: (1) The goal of enjoying a movie in a theater may be set in the control system via the basal ganglia predicting reward, (2) a series of actions get you to the theater and the movie begins, (3) anxiety resulting from a hyperactive amygdala (Phan and others 2006) may get in the way of enjoying the movie (the goal), initiating a search by the control system to find a functional connectivity configuration that reduces hyperactivity in the amygdala (i.e., inhibition of the amygdala by the control system). Such control system regulation strategies may ultimately facilitate fear extinction via orbitofrontal-amygdala circuits (Schiller and Delgado, 2010).

An alternative feedback control mechanism may also result in a reduction of amygdala hyperactivity. This mechanism—indirect feedback control (Fig. 4B)—involves control of a process that (1) is accessible to the control system and (2) is incompatible with the to-be-controlled process. In the social phobia example, a control system strategy of regulating breathing (a process readily accessible by the control system) can result in reduced amygdala hyperactivity, perhaps because of strong connections in the limbic system between breathing and mental state. Indirect feedback control can also involve more explicit changes to the environment (e.g.,
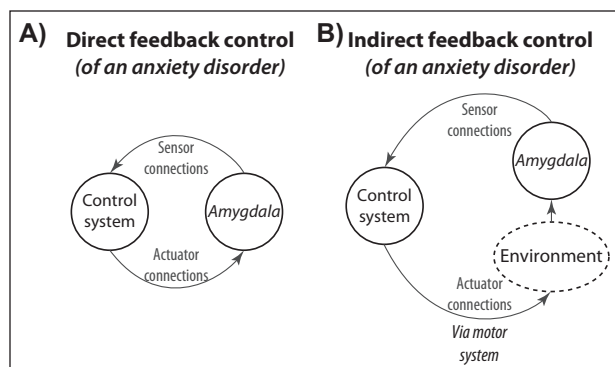
Figure 4. Direct and indirect feedback control. An anxiety disorder (e.g., social phobia) is illustrated as an example of two ways that the control system could regulate symptoms of anxiety. (A) Direct feedback control is illustrated by direct monitoring and inhibition of a hyperactive amygdala via brain connectivity. Note that direct feedback control can also involve brain connectivity over multiple synapses (e.g., control system to orbitofrontal cortex to amygdala). (B) Indirect feedback control is illustrated by direct monitoring and indirect inhibition of a hyper-active amygdala via changes to the environment. These changes are implemented via the motor system. Examples include (1) deep breathing, which changes sympathetic versus parasympathetic balance and indirectly influences amygdala and (2) moving to a room that is comforting, thereby removing any environmental stimuli contributing to the hyperactive amygdala. A combination of direct and indirect feedback control strategies is likely the most effective, though implementing multiple control strategies would require a highly effective control system.

leaving the theater to watch a movie at home) to achieve a goal. There are likely indirect feedback control processes that apply to other mental diseases as well.

Though two distinct feedback control mechanisms were described, they both involved the control system as central to responding to feedback in a goal-driven manner. This suggests there are likely numerous scenarios where an intact and robust control system would be highly useful for regulating the symptoms of mental disease.

Control System Disruption as Cause or Consequence of Mental Disease

The flexible hub framework postulates that many mental diseases (especially secondary control diseases) are not caused by control system disruption. Rather, consistent with an immune system analogy, the theory postulates that most cases of mental disease could be ameliorated or perhaps even prevented with an especially effective control system. This suggests that control system disruption may nonetheless play a causal and critical role in a variety of mental diseases, with implications for functional outcomes.

Critically, however, the reverse causal direction is likely also present: suffering from a mental disease may disrupt

control system processes. We hypothesize this causal direction because the dedication of the control system to regulating symptoms likely reduces the system's spare capacity in other domains, such as solving problems in daily life or on a test of cognitive/executive control abilities in a laboratory. Reduced ability to deal with the problems of daily life is of course itself a symptom. The predicted influence of reduced control system capacity on daily life is consistent with observations that cognitive control abilities are reduced in a variety of mental illnesses (Barch 2005; Bowie and others 2006; Lee and others 2012) and that such disruptions of cognitive control abilities profoundly affect daily life (Bowie and others 2006). Note that such indirect reductions in control system capacity because of attempts to implement any given feedback control strategy (e.g., suppress negative thoughts) likely reduces capacity for discovering more effective feedback control strategies (e.g., deep breathing, cognitive reappraisal). The consequence of this may in some cases be a kind of "stuck" state, in which mental health is unlikely to improve without external intervention.

More generally, the reduction of control system capacity by symptom regulation demands is consistent with well-known capacity limits of cognitive control abilities (Schmeichel and others 2008) and the control system that implements those abilities (Buschman and others 2011; Mitchell and Cusack 2008). There are a variety of factors that influence cognitive control capacity. Some factors that reduce control capacity include excessive stress (Sato and others 2012), cognitive load (e.g., pursuit of other goals, rumination) (Brinker and others 2013), poverty (possibly via cognitive loading) (Mani and others 2013), and negative affect (Kleider and others 2009). Some factors that increase cognitive control capacity include motivation (reward prediction) (Locke and Braver 2008), optimal levels of stress (Vijayraghavan and others 2007), focused goals (Locke and Latham 2006), effective strategies for the goal at hand (Cole and others 2013a), and adaptive habits (to reduce cognitive load) (Chein and Schneider 2012). The multitude of factors that influence control system capacity suggests that cognitive control capacity can vary substantially both within and across individuals as these factors change and interact. Furthermore, this suggests there are multiple means for increasing control system capacity and therefore facilitate functional outcomes during treatment (see Fig. 2).

Psychotherapy as Augmenting the Control System

Psychotherapy is often effective in improving mental health (Knekt and others 2013; Seligman 1995). We suggest this may be primarily because of improvements in goal pursuit—psychotherapy may enhance the control
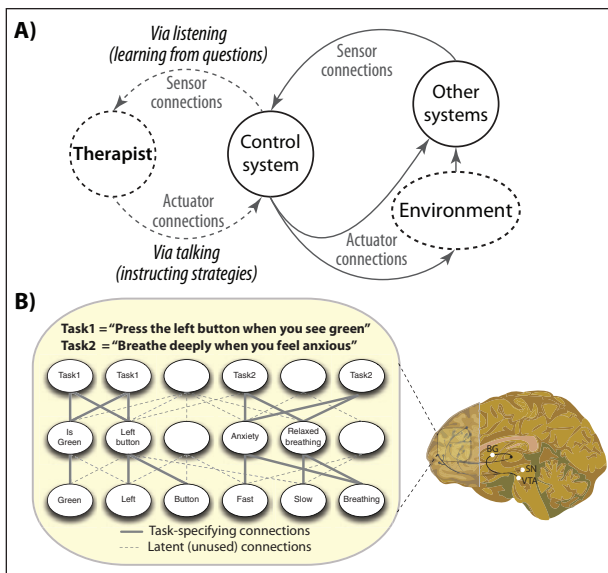
Figure 5. Rapid instructed task learning, flexible hubs, and psychotherapy. (A) Psychotherapy is illustrated as augmenting the control system's search for ways to regulate symptoms. The therapist uses listening (with questions) to detect the nature of symptoms (and previous attempts to regulate them), which informs instructed strategies that are ultimately implemented by the control system via rapid instructed task learning (Cole and others 2013a). A specific example of this therapeutic process may be exposure-response prevention with cognitive-behavioral therapy elements designed for obsessive-compulsive disorder (Abramowitz and Arch 2014). (B) Potential neural population mechanisms within LPFC for rapid instructed task learning (Cole and others 2013a). Verbal instructions activate primitive components (bottom) and their relations are built via local connectivity to build task procedures on the fly. Substantia nigra (SN), ventral tegmental area (VTA), and other basal ganglia (BG) (O'Reilly and Frank 2006) help update LPFC with new instructions (see Figure 1D). Task 1 is a typical cognitive laboratory task, involving an arbitrary stimulus-response association. Task 2 is an adaptive real-world strategy used in psychotherapy to reduce anxiety. Both tasks are illustrated using the same mechanisms. Note that the mechanisms are simplified for illustration (e.g., representations overlap across neural populations in LPFC) (Cole and others 2013a; Rigotti and others 2013).

system by augmenting its feedback control mechanism (Fig. 5A). It may be that if the control system is not successful in regulating aberrant representations in other systems a therapist can initiate a feedback control loop to facilitate the existing feedback control implemented by the control system. This may involve asking questions to gain information about the symptoms and previous attempts to regulate them, followed by instructions for strategies to try. This is the same goal-directed search process described above (Fig. 1D), but augmented by a therapist's knowledge and experience. Thus, a social phobia patient with especially high amygdala hyperactivity

(Phan and others 2006) and/or a somewhat ineffective control system can be instructed on how to detect anxiety (improved selection of sensor connections) and to initiate a deep breathing strategy whenever anxiety is present (improved selection of actuator connections). This can speed up the search for a strategy (i.e., a set of sensor and actuator connections) to regulate symptoms.

This account is highly compatible with recently developed theories of the neural mechanisms of psychotherapy (Clark and Beck 2010; DeRubeis and others 2008). These theories are based on recent observations that successful psychotherapeutic treatments of depression and anxiety disorders are associated with increased activity in control system regions and decreased activity in amygdala and other emotion processing regions (Browning and others 2010; Goldin and others 2009). These models of therapeutic mechanisms (and the flexible hub framework) are also consistent with observations that the control system is involved in goal-directed thought (including emotion) suppression (Wager and others 2008). Building on these theories, however, the flexible hub framework includes more specific neural mechanisms while also providing a more general account across mental disorders and in the maintenance of mental health in healthy individuals. These differences may prove important for gaining further insight into the mechanisms of psychotherapy, as well as insight into the interaction of psychotherapy with psychopharmacology and personal efforts by patients to reduce their symptoms.

In addition to the global connectivity and feedback control mechanisms described above, the flexible hub framework postulates neural mechanisms at the level of local neural populations (Fig. 5B). These mechanisms describe how novel procedures can be rapidly learned from instructions—rapid instructed task learning (Cole and others 2013b). This skill may be especially important for psychotherapy, given psychotherapy's reliance on verbal instructions to achieve cognitive and behavioral change. The key idea is that we learn a set of cognitive components early in life (e.g., monitoring breathing, detecting anxiety, controlling breathing) that can be rapidly recombined via connectivity in the control system into novel procedures through instructions. This ability likely allows for the cognitive flexibility necessary for psychotherapy to be effective.

Note that there are some important nuances to this framework. First, it is possible for the control system itself to have faulty strategies that actually exacerbate symptoms rather than improve them. For instance, previously small reductions in negative affect from eating may result in the maladaptive control strategy of binge eating to regulate negative affect (Spitzer and others 1993), causing more negative affect in the long run. Similarly, control system attempts to regulate anxiety can result in

panic attacks if attending to the symptom elevates anxiety (in a vicious cycle) (Pauli and others 1991). Such cases are likely especially difficult to correct given that the control system's feedback control "program" is itself compromised (e.g., like an autoimmune disorder). It is likely that hierarchical control can come into play in such cases—the higher order control of strategies based on more generalized thinking, which may reflect the organization of the control system (Badre 2008). Individuals in these situations may benefit the most from "control system augmentation" by a therapist, since this can help reprogram the control system to use more effective symptom regulation strategies.

As a second nuance, the framework might apply more for some forms of psychotherapy than others. In particular, it may apply best to cognitive-behavioral therapy (Butler and others 2006), which combines cognitive therapy (focusing on regulating thoughts and emotions) and behavioral therapy (focused on regulating actions/behavior). This is because the two aspects of cognitive-behavioral therapy correspond to using both available types of actuator connections (Figs. 4 and 5B)—direct control-to-symptom connections (via cognitive/affective regulation) and indirect control-to-symptom connections (via behavior/environment regulation). This framework may also apply to even highly distinct forms of psychotherapy, however. For instance, a variety of psychotherapies (e.g., acceptance and commitment therapy) use mindfulness meditation, which involves focusing attention and accepting events as they occur (Khoury and others 2013). Focusing attention is a core function of the control system, while emotional reappraisal to allow for acceptance of events is also thought to be mediated by the control system (Ochsner and others 2002). Consistent with this, the control system is active during mindfulness meditation (Chiesa and others 2013). Importantly, however, the control system becomes less active after extensive practice (Chiesa and others 2013), suggesting the ultimate goal of meditation is for the control system to train other systems to "automatically" facilitate a mindful state (i.e., attention to the moment without judgment)—a state incompatible with a variety of harmful dysfunctions. We review evidence that the control system can train other systems to achieve automaticity in the next section.

Predictions of the Flexible Hub Framework for Future Research

The flexible hub theory makes a variety of predictions cutting across mental disorders. We outline what we see as some of the more important predictions for future research to test, which may lead to discoveries that can improve understanding of disease mechanisms and lead to improved therapeutic outcomes.

Perhaps the clearest prediction is that control system disruptions will be associated with an even larger set of mental disorders than already covered here. Furthermore, details regarding the nature of those control system disruptions are predicted by the flexible hub feedback control mechanism described above. For instance, the framework predicts that control system connectivity with a variety of systems—and especially those systems whose dysfunction is primarily causing the mental disorder— will be lower in most individuals with virtually any form of mental disorder. While this is a broad prediction, we suggest it will have a very specific manifestation depending on the nature of the behavioral symptoms involved.

We have emphasized control system disruption in terms of large-scale connectivity, yet the system could be disrupted in other ways as well. For instance, the control system could be disrupted in terms of local connectivity (Chen and others 2012), genetics (Esslinger and others 2009), local protein dysregulation (Drummond and others 2013), or electrophysiological activity dynamics (Wölwer and others 2012). It will be important for future research to investigate these different possible means of disruption (and possible treatments) in patients with a variety of mental diseases as well as in animal models.

A particularly important prediction for early intervention is that control system disruption early in life may be predictive of mental disorders later. This is in line with recent findings that reduced childhood cognitive control abilities are associated with worse outcomes in autism and attention deficit hyperactivity disorder (Johnson 2012), and are predictive of the development of borderline personality disorder (Ayduk and others 2008). Also consistent is the observation that cognitive control abilities early in life predict later mental illness more generally (Mischel and others 2011; Moffitt and others 2011). The key idea behind this prediction is that those with a strong control system throughout life are better able to regulate the onset of symptoms (i.e., aberrant brain activity). This protective aspect of the control system is also in line with the analogy that the control system is akin to an "immune system of the mind."

A corollary of the previous prediction is that many healthy individuals likely have subclinical symptoms of mental disorders that remain subclinical only because the control system successfully regulates them (see lower right corner of Fig. 2). This prediction, if true, has profound consequences for our understanding of mental illness and the (potentially minor) distinctions between those diagnosed with a mental disorder versus not. This prediction is also associated with even more specific hypotheses: that some healthy individuals likely have reduced cognitive control abilities because of the need to constantly regulate symptoms, and that many individuals likely experience symptoms of mental disorders at some

point in life—especially while the control system is developing. Consistent with this expectation, it was recently found that most mentally healthy individuals have at least one symptom of a mental disorder prior to adulthood (Copeland and others 2011).

If the control system regulates symptoms as suggested here, it may seem as though such regulation would need to go on indefinitely once symptoms arise in a mental disorder. Importantly, however, there is evidence that the control system is able to "train" posterior regions to "automatically" implement simple goal-compatible processes over time (Chein and Schneider 2005, 2012; Miller and Cohen 2001). This suggests that an effective control system may be able to utilize feedback control to reduce neural dysfunctions over the long term via training to achieve automaticity. For example, the control system may reduce an anxious individual's amygdala hyperactivity so often that long-term depression among amygdala synapses reduces the neural dysfunction. As another example, a control strategy to breathe deeply whenever stressful situations arise (to reduce amygdala hyperactivity dynamically) may become "automatic" and independent of the control system over time, as functional connectivity between stress-associated sensation representations and deep breathing representations get strengthened.

Finally, the flexible hub framework makes three predictions related to external manipulation of control systems. First, the theory predicts that increasing control system activity—possibly via cognitive training (Mackey and others 2013), transcranial stimulation, or pharmacology—would improve symptoms in a variety of mental diseases. Second, improving control system integrity (e.g., improving within-system or global connectivity)—again via cognitive training (Mackey and others 2013), transcranial stimulation, or pharmacology—would reduce symptoms in a variety of mental diseases. Third, neurofeedback (Weiskopf 2011) may be an especially effective approach to enhance control system feedback control to reduce symptoms in a variety of diseases. It will be important to test these possibilities experimentally as they make clear predictions regarding potential ways to enhance treatment of a broad range of mental diseases.

We have outlined an extension of the flexible hub theory (Cole and others 2013b) – and theories it is built upon (Miller and Cohen 2001) – to account for recent findings in the neuroscience of a variety of mental diseases. This novel framework is compatible with a broad sampling of recent findings indicating a central role of the control system in mental disease. Nevertheless, more evidence is necessary to verify the framework by testing its predictions. For instance, more before-and-after treatment studies would be useful in establishing a causal role of control system integrity in mental disease and treatment outcomes. Similarly, longitudinal studies across diagnoses will be vital to arbitrate the causal role of the control system in different conditions. Furthermore, direct manipulations of the control system, such as via transcranial stimulation (Fox and others 2012), pharmacology (Anticevic and others 2012b), or neurofeedback (Weiskopf 2011) could provide not only strong evidence for a causal role of the control system in mental disease but also potential novel treatments. Additionally, while the current account is positioned at the level of neural systems, linking the proposed framework across levels of analyses will be important for a complete understanding of the proposed mechanisms. This can be done, for instance, by incorporating detailed pharmacological probes (Krystal and others 2003) and biophysically based computational modeling studies (Wang 2010) of specific cognitive processes into the experimental repertoire when testing this theory. Generally, discovering more about the basic mechanisms of the control system will provide critical tests and extensions of the framework, which can in turn facilitate clinical studies seeking to understand the exact computational dynamics by which the control system may facilitate regulation of symptoms in each of a variety of mental diseases.

Finally, the flexible hub theory suggests a potentially efficient means to achieving effective new treatments by focusing basic and clinical research on the control system, given the potential to apply our understanding of this system to improve treatment outcomes across a variety of mental diseases simultaneously.

Declaration of Conflicting Interests

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